

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>A61P 27/06, A61K 31/4045,</b> <b>31/137, 31/498, 31/4168</b>	<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 00/16761</b> <b>(43) International Publication Date:</b> 30 March 2000 (30.03.00)
<b>(21) International Application Number:</b> PCT/US99/19888 <b>(22) International Filing Date:</b> 3 September 1999 (03.09.99)  <b>(30) Priority Data:</b> 60/101,067 18 September 1998 (18.09.98) US  <b>(71) Applicant (for all designated States except US):</b> ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> MAY, Jesse, A. [US/US]; 4132 Hildring Drive East, Fort Worth, TX 76109 (US). DEAN, Thomas, R. [US/US]; 101 Meadow View Court, Weatherford, TX 76087 (US). SHARIF, Najam, A. [GB/US]; 7 Courtney Court, Arlington, TX 76015 (US).  <b>(74) Agents:</b> YEAGER, Sally, S. et al.; R & D Counsel Q-148, Alcon Laboratories, Inc., 6201 South Freeway, Fort Worth, TX 76134-2099 (US).		<b>(81) Designated States:</b> AU, BR, CA, CN, JP, KR, MX, TR, US, ZA, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>  <b>(88) Date of publication of the international search report:</b> 25 May 2000 (25.05.00)
<b>(54) Title:</b> SEROTONERGIC 5HT <sub>2</sub> AGONISTS FOR TREATING GLAUCOMA		
<b>(57) Abstract</b>  Compounds with 5HT <sub>2</sub> receptor agonist activity useful for treating glaucoma, including lowering intraocular pressure. Compositions and methods for their use are also disclosed.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LJ	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## INTERNATIONAL SEARCH REPORT

Inter. Appl. No.  
PCT/US 99/19888

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61P27/06 A61K31/4045 A61K31/137 A61K31/498 A61K31/4168

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HUANG X ET AL: "5-HT2 receptor-mediated potentiation of dopamine synthesis and central serotonergic deficits." EUROPEAN JOURNAL OF PHARMACOLOGY, (1993 JUL 20) 238 (2-3) 291-6. , XP000878592 abstract paragraph '02.3!	8-11
X	GLENNON: "a comparison of the behavioural properties of..." BIOLOGICAL PSYCHIATRY, vol. 18, no. 4, 1983, XP000878692 page 1 figure 1 page 496, line 1 - line 12 --- -/-	8-11

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

3 March 2000

Date of mailing of the international search report

15/03/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Bonzano, C

## INTERNATIONAL SEARCH REPORT

Inter. Appl. Application No

PCT/US 99/19888

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 29074 A (LILLY CO ELI) 26 September 1996 (1996-09-26) page 12, line 18 -page 13, line 23 claims 10,11	8-11
X	MONGEAU R. ET AL: "Activation of 5-HT <sub>3</sub> receptors enhances the electrically evoked release of <sup>3</sup> H:noradrenaline in rat brain limbic structures." EUROPEAN JOURNAL OF PHARMACOLOGY, (1994) 256/3 (269-279). , XP000884750 paragraph '03.4! figure 5	8,11-14
A	WO 98 18458 A (OSBORNE NEVILLE ;DESANTIS LOUIS JR (US); ALCON LAB INC (US); SALLE) 7 May 1998 (1998-05-07) page 2, line 23 -page 3, line 23	1-14
A	WO 97 33579 A (GLAXO GROUP LTD ;DESAI JEREMY BHARAT (GB); LACEY LAURENCE FRANCIS) 18 September 1997 (1997-09-18) page 4, line 1 - line 10	1-14
A	WO 94 03162 A (GLAXO GROUP LTD ;BIRCH PHILLIP JOHN (GB)) 17 February 1994 (1994-02-17) abstract; claims 1-7	1-14
A	OSBORNE N.N.: "Serotonin and melatonin in the iris/ciliary processes and their involvement in intraocular pressure." ACTA NEUROBIOLOGIAE EXPERIMENTALIS, (1994) 54/SUPPL. (57-64). , XP000878634 page 61, column 1 -column 2	1-14
A	GUPTA Y K ET AL: "THERAPEUTIC POTENTIALS OF 5-HT RECEPTOR MODULATORS" INDIAN JOURNAL OF PHARMACOLOGY,XX,XX, vol. 26, no. 2, 1 June 1994 (1994-06-01), pages 94-107, XP000571272 ISSN: 0253-7613 page 102, paragraph E	1-14
A	CHU, TEH-CHING (1) ET AL: "8OH-DPAT-induced ocular hypotension: Sites and mechanisms of action." EXPERIMENTAL EYE RESEARCH, (AUG., 1999) VOL. 69, NO. 2, PP. 227-238. , XP000879248 page 235, column 2, paragraph 2	1-14

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/19888

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 1-7  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:  
SEE FURTHER INFORMATION PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

Present claims 1-3, 5-10,12-14 relate to compounds defined by reference to a desirable pharmacological property, namely the activity as 5HT2 agonists and the activity as: beta-blockers, carbonic anhydrase inhibitors, alpha2 agonists and mitotics.

The claims cover all compounds having this characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is not fully possible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to their pharmacological profiles. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds structurally identified in claims 4,7,11,14, with due regard to the general idea underlying the present invention.

Claims searched completely: 4,11.

Claims searched incompletely: 1-3,5-10,12-14.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/19888

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9629074 A	26-09-1996	AU 5528996 A	08-10-1996
WO 9818458 A	07-05-1998	AU 4249297 A	22-05-1998
WO 9733579 A	18-09-1997	AU 2104097 A	01-10-1997
WO 9403162 A	17-02-1994	AU 4705193 A	03-03-1994
		EP 0655912 A	07-06-1995
		JP 7509476 T	19-10-1995
		US 5693654 A	02-12-1997
		ZA 9305522 A	13-06-1994

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification<sup>7</sup> :</b> <b>A61K 31/00</b>	<b>A2</b>	<b>(11) International Publication Number:</b> <b>WO 00/16761</b> <b>(43) International Publication Date:</b> 30 March 2000 (30.03.00)
<b>(21) International Application Number:</b> PCT/US99/19888 <b>(22) International Filing Date:</b> 3 September 1999 (03.09.99)  <b>(30) Priority Data:</b> 60/101,067 18 September 1998 (18.09.98) US  <b>(71) Applicant (for all designated States except US):</b> ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> MAY, Jesse, A. [US/US]; 4132 Hildring Drive East, Fort Worth, TX 76109 (US). DEAN, Thomas, R. [US/US]; 101 Meadow View Court, Weatherford, TX 76087 (US). SHARIF, Najam, A. [GB/US]; 7 Courtney Court, Arlington, TX 76015 (US).  <b>(74) Agents:</b> YEAGER, Sally, S. et al.; R & D Counsel Q-148, Alcon Laboratories, Inc., 6201 South Freeway, Fort Worth, TX 76134-2099 (US).		<b>(81) Designated States:</b> AU, BR, CA, CN, JP, KR, MX, TR, US, ZA, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> SEROTONERGIC 5HT <sub>2</sub> AGONISTS FOR TREATING GLAUCOMA  <b>(57) Abstract</b>  Compounds with 5HT <sub>2</sub> receptor agonist activity useful for treating glaucoma, including lowering intraocular pressure. Compositions and methods for their use are also disclosed.		



**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MY	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## SEROTONERGIC 5HT<sub>2</sub> AGONISTS FOR TREATING GLAUCOMA

The present invention is directed to the use of compounds with serotonergic 5HT<sub>2</sub> agonist activity (Compound) to treat glaucoma, which includes lowering intraocular pressure.

### Background of the Invention

Serotonin (5-hydroxytryptamine; 5HT) is an endogenous biogenic amine with a well defined neurotransmitter function in many tissues of the body including the eye [Zifa and Fillion, *Pharmacol. Rev.*, **44**, 401 (1992); Hoyer et al., *Pharmacol. Rev.*, **46**, 157 (1994); Tobin et al., *J. Neurosci.*, **8**, 3713 (1988)].

5HT can interact with at least seven major 5HT receptors (5HT<sub>1</sub> - 5HT<sub>7</sub>) and additional subtypes within these families to initiate intracellular biochemical events such as stimulation of second messengers (e.g. cAMP, inositol trisphosphate) eventually leading to the final biological response, for example, tissue contraction or hormone release, etc. [Hoyer et al., *supra*; Martin et al., *Trends Pharmacol. Sci.*, **19**, 2 (1998)]. Receptor subtypes within the 5HT<sub>1</sub> family are negatively coupled to adenylyl cyclase (AC) and cause inhibition of cAMP production, while 5HT<sub>4</sub>, 5HT<sub>6</sub>, and 5HT<sub>7</sub> receptors are positively coupled to AC and thus stimulate cAMP production when activated by 5HT [Martin et al., *supra*]. The 5HT<sub>3</sub> receptor is unique in that it couples to an ion channel which gates sodium, potassium, and calcium [Hoyer et al., *supra*].

The receptors in the 5HT<sub>2</sub> family are positively coupled to phospholipase C (PLC) and thus generate inositol phosphates and mobilize intracellular calcium when activated by 5HT. The 5HT<sub>2</sub> receptor classification consists of the 5HT<sub>2A</sub>, 5HT<sub>2B</sub>, and 5HT<sub>2C</sub> receptor subtypes, all of which have highly homologous amino acid sequences. The receptor previously referred to as 5HT<sub>1C</sub> in an earlier nomenclature (prior to about 1990), has been reclassified as the 5HT<sub>2C</sub> receptor because of its greater similarity with other PLC coupled receptors of the

5HT<sub>2</sub> family, based on molecular cloning and its pharmacological characteristics (Hoyer, et al, 1994).

Serotonergic nerves innervate the eye [Tobin et al., *J. Neurosci.*, **8**, 3713 (1988)] and  
5 5HT has been found in the aqueous humor of human eyes [Martin et al., *Ophthalmol.*, **95**,  
1221 (1988)]. In addition, receptor binding sites for [<sup>3</sup>H]5HT have been demonstrated and  
pharmacologically characterized in the iris-ciliary body (ICB) of rabbits [Mallorga and  
Sugrue, *Curr. Eye Res.*, **6**, 527 (1987) and Chidlow et al., *Invest. Ophthalmol. Vis. Sci.*, **36**,  
2238 (1995)]. These 5HT binding sites have been shown to be functionally coupled to  
10 second messenger generation in rabbits [Tobin and Osborne, *J. Neurochem.*, **53**, 686 (1989)  
and Tobin et al., *J. Neurosci.*, *supra*]. In the human ICB these binding sites are characterized  
as 5HT<sub>1A</sub> and 5HT<sub>2</sub> receptors [Barnet and Osborne, *Exp. Eye Res.*, **57**, 209 (1993)]. In  
addition, the presence of mRNAs for 5HT<sub>1A</sub> and 5HT<sub>7</sub> receptors in the rabbit ICB have been  
reported [Chidlow et al., *Invest. Ophthalmol. Vis. Sci.*, *supra* and Osborne and Chidlow,  
15 *Ophthalmologica*, **210**, 308 (1996)]. The precise functions of these receptors in the eye are  
unknown.

5HT or 5-carboxamidotryptamine (5-CT) topically applied to the rabbit eye raise  
intraocular pressure (IOP) [Meyer-Bothling et al., *Invest. Ophthalmol. Vis. Sci.*, **34**, 3035  
20 (1993)]. By contrast, another group has shown that topically applied 5HT decreased IOP in  
the rabbit; however, when 5HT was administered to the rabbit intracamerally it resulted in an  
increase in IOP and caused breakdown of the blood-aqueous barrier [Krootila et al., *J. Ocular  
Pharmacol.*, **3**, 279 (1987)]. In addition, the 5HT uptake inhibitor, fluoxetine (Prozac<sup>®</sup>), also  
raises IOP in human subjects upon oral administration [Costagliola et al., *Br. J. Ophthalmol.*,  
25 **80**, 678 (1996)] and may cause glaucoma [Ahmad *Ann. Pharmacother.*, **25**, 436 (1992)].  
However, the 5HT receptor subtype(s) involved in the IOP-elevating effects of 5HT, 5-CT  
and fluoxetine are unknown.

Studies conducted in rabbits with 8-hydroxy DPAT and MKC-242 (5HT<sub>1A</sub> agonists)  
30 have shown these compounds lower IOP [Osborne and Chidlow *Ophthalmologica*, **210**, 308  
(1996), and EP 0771563-A2]. In addition, 5-methylurapidil (5HT<sub>1A</sub> agonist) lowered IOP in  
glaucomatous monkeys [Wang et al., *Curr. Eye Res.*, **16**, 679 (1997)]. Both MKC-242 and 5-

methylnurapidil are relatively potent  $\alpha_1$  receptor antagonists ( $\alpha_1$  antagonists are known to lower IOP in rabbits, monkeys, and man). The mechanism of action for lowering IOP by 5-methylnurapidil has been attributed to its  $\alpha_1$  antagonist activity and not its 5HT<sub>1A</sub> agonist activity [Wang et al., *Invest. Ophthalm. Vis. Sci.*, **39**(Suppl), 2236 (1998)]. U.S. Patent No. 5,693,654, discloses 5HT<sub>1</sub>-like (now designated 5HT<sub>1D</sub>) receptor agonists, such as sumatriptan, for lowering IOP. WO92/20338 discloses certain 5HT<sub>1A</sub> antagonists for the treatment of glaucoma.

Methysergide (5HT<sub>2</sub> antagonist, but with other activities) lowered IOP in rabbits [Krootila et al., *Exp. Eye Res.*, *supra*]. Ketanserin (5HT<sub>2A/C</sub> antagonist), also with significant  $\alpha_1$  antagonist activity, lowers IOP in rabbits and man [Chan et al., *J. Ocular Pharmacol.*, **1**, 137 (1985) and Costagliola et al., *Exp. Eye Res.*, **52**, 507 (1991)]. Saprogrelate (5HT<sub>2A</sub> antagonist) lowers IOP in rabbits and in man when dosed topically or orally [Mano et al., *Invest. Ophthalm. Vis. Sci.*, **36**(Suppl), 3322 (1995) and Takenaka et al., *Invest Ophthalm. Vis. Sci.*, **36**(Suppl), 3390 (1995)]. EP 522226 and U.S. Patent No. 5,290,781 disclose the use of ketanserin and its derivatives for treating ocular hypertension. U.S. Patent Nos. 5,290,781 and 5,106,555 disclose the use of certain 5HT<sub>2</sub> antagonists for lowering IOP. U.S. Patent No. 5,652,272 discloses saprogrelate for reducing IOP. U.S. Patent No. 5,538,974 discloses ophthalmic compositions of certain 5HT<sub>2</sub> antagonists for lowering IOP. WO/9911619 discloses 5HT<sub>2A</sub> antagonists which may be efficacious in treating glaucoma.

U.S. Patent No. 5,011,846 discloses certain 5HT<sub>3</sub> receptor antagonists for treating glaucoma.

WO 97/17345 discloses that particular compounds with 5HT<sub>4</sub> serotonergic receptor agonist or antagonist activity are useful for treating psychiatric, gastrointestinal, lower urinary, and cardiovascular disorders. The publication mentions the compounds may also be useful for glaucoma.

As evidenced by the previous discussion, it is not clear which serotonergic receptor activity is responsible for lowering IOP. Moreover, a number of these compounds are known

to have activity at non-serotonergic receptors which are known to be involved in lowering IOP.

### Summary of the Invention

The present invention is directed to the use of compounds with 5HT<sub>2</sub> receptor agonist activity to treat glaucoma, which includes lowering intraocular pressure. Compositions of the compounds are contemplated for such uses.

### Detailed Description Preferred Embodiments

Unexpectedly, it has been found that serotonergic compounds which possess agonist activity at 5HT<sub>2</sub> receptors effectively lower and control elevated IOP and are useful for treating glaucoma.

Specific compounds which exemplify the present invention include: 1) (R)-4-iodo-2,5 dimethoxy- $\alpha$ -methyl-benzeneethanamine [(R)-DOI], the prototypical selective 5HT<sub>2</sub> agonist which is not selective amongst the 5HT<sub>2</sub> receptor subtypes [Baxter et al., *Trends. Pharmacol. Sci.*, **16**, 105 (1995)]; 2)  $\alpha$ -methyl-serotonin, a potent 5HT<sub>2</sub> agonist with modest receptor subtype selectivity: 5HT<sub>2B</sub>>5HT<sub>2C</sub>>5HT<sub>2A</sub> [Baxter, et al., *supra*]; 3) 5-methoxy- $\alpha$ -methyltryptamine, with a profile similar to that of  $\alpha$ -methyl-serotonin [Nichols et al., *J. Med. Chem.*, **31**, 1406 (1998)]. The following references are not limiting, but rather exemplify Compounds useful according to the present invention and are incorporated herein by reference: U.S. Patent Nos. 5,861,425; 5,646,173; 5,578,612; 5,571,833; 5,545,644; 5,494,928; 4,659,706 and 4,487,773; published European Patent Specification No. 863,136; published International Patent Application Nos. WO98/56768; WO98/31354; WO98/30548; WO98/30546. Additionally, compounds disclosed in the following publications further exemplify Compounds useful according to the present invention and are also incorporated herein by reference: Parker et al, *J. Med. Chem.* **41**, 5148 (1998); Vangveravong et al, *J. Med. Chem.* **41**, 4995 (1998); Albertini et al, *Mutagenesis*, **13**, 397 (1998); Monte et al, *J. Med. Chem.* **40**, 2997 (1997); Bös et al., *Eur. J. Med. Chem.*, **32**, 253 (1997); Bös et al., *J. Med. Chem.*, **40**, 2762 (1997); Monte et al, *J. Med. Chem.* **39**, 2952 (1996); Glennon et al., *J. Med.*

*Chem.*, **37**, 1929 (1994); Macor et al, *Tetrahedron Lett.* **35**, 45 (1994); Macor et al, *J. Med. Chem.* **35**, 4503 (1992); Macor et al. *J. Med. Chem.*, **35**, 3625 (1992); Glennon et al, *J. Med. Chem.* **35**, 734 (1992); Seggel et al. *J. Med. Chem.* **33**, 1032 (1990).

5 It is recognized that many of the aforementioned Compounds have asymmetric atoms, therefore all enantiomers and diastereomers are contemplated. Also contemplated are pharmaceutically acceptable salts as well as the free bases of the Compounds. The Compounds are administered to the eye (e.g., topically, intracamerally, or via an implant). The Compounds are preferably incorporated into topical ophthalmic formulations for delivery  
10 to the eye. The Compounds may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution. Ophthalmic solution formulations may be prepared by dissolving a Compound in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may  
15 include an ophthalmologically acceptable surfactant to assist in dissolving the Compound. Furthermore, the ophthalmic solution may contain an agent to increase viscosity, such as, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like, to improve the retention of the formulation in the conjunctival sac. Gelling agents can also be used, including, but not limited to, gellan  
20 and xanthan gum. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the active ingredient in a hydrophilic base prepared from the combination of, for example, carbopol-940, or the like, according to the published formulations for analogous  
25 ophthalmic preparations; preservatives and tonicity agents can be incorporated.

The Compounds are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 5 to 8. The Compounds will normally be contained in these formulations in an amount 0.01% to 5% by weight, but preferably in an amount of 0.25% to  
30 2% by weight. Thus, for topical presentation 1 to 2 drops of these formulations would be delivered to the surface of the eye 1 to 4 times per day according to the routine discretion of a skilled clinician.

The Compounds can also be used in combination with other agents for treating glaucoma, such as, but not limited to,  $\beta$ -blockers, prostaglandins, carbonic anhydrase inhibitors,  $\alpha_2$  agonists and miotics. The Compounds can also be used with calcium channel blockers and antagonists for metabotropic and ionotropic glutamate receptors and/or antagonists for their associated binding sites, such as, the polyamine and strychnine-insensitive glycine sites. These agents may be administered topically, but usually systemically.

A particularly preferred combination includes the use of a Compound with an  $\alpha_2$  adrenergic agent, such as, apraclonidine or brimonidine or their pharmaceutically acceptable salts.

Compounds useful in this invention can be identified using methodology well known to one skilled in the art. The selection is made first by using a 5HT<sub>2</sub> receptor binding assay, an example of which is described below. Compounds of this invention possess high affinity for 5HT<sub>2</sub> receptors (IC<sub>50</sub> or K<sub>i</sub> values of about 20nM or less and this affinity is higher than at other 5HT receptors). The second part of this selection is made based on the functional activity of the compound as described below. Compounds of this invention possess agonist EC<sub>50</sub> values of about 1 $\mu$ M or less. Antagonists are not contemplated in this invention.

Both of these methods are believed to be the best way to identify a compound that would be useful according to this invention; however, it is important to note that some compounds that are identified by these methods may not be as desirable as others as commercial products. One must take into account the nature of the compound in question in terms of its structure, physical properties – e.g., solubility, lipophilicity, and chemical stability and its susceptibility to be metabolized to an inactive compound (or compounds) within the eye. The impact of these parameters is well known to one skilled in the art and can be determined using methods well known in the art.

In addition to the above discussion, certain 5HT<sub>2</sub> agonists such as DOI, its isomers, and related compounds are known to cause central nervous system (CNS) side effects in man

when dosed systemically. In the present invention it is believed that the Compounds can be dosed topically, at a low enough dose to lower and control IOP, but not cause unwanted CNS side effects which may be associated with some Compounds. Some Compounds are particularly desirable because their physical properties keep them from penetrating the CNS and causing side effects. Also, certain Compounds of this invention may cause local irritation and discomfort upon topical ocular administration that render them less desirable than other more comfortable compounds. This can be readily determined using methods well known in the art.

## EXAMPLE 1

### 5HT<sub>2</sub> Receptor Binding Assay

In order to determine the relative affinities of serotonergic compounds at the 5HT<sub>2</sub> receptors, their ability to compete for the binding of the agonist radioligand [<sup>125</sup>I]DOI to brain 5HT<sub>2</sub> receptors is determined as described below with minor modification of the methods of Johnson et al. (*Neuropharmacology*, **26**, 1803 (1987)). Aliquots of post mortem rat or human cerebral cortex homogenates (400 µl) dispersed in 50 mM TrisHCl buffer (pH 7.4) are incubated with [<sup>125</sup>I]DOI (80 pM final) in the absence or presence of methiothepin (10 µM final) to define total and non-specific binding, respectively, in a total volume of 0.5 ml. The assay mixture is incubated for 1hr at 23°C in polypropylene tubes and the assays terminated by rapid vacuum filtration over Whatman GF/B glass fiber filters previously soaked in 0.3% polyethyleneimine using ice-cold buffer. Test compounds (at different concentrations) are substituted for methiothepin. Filter-bound radioactivity is determined by scintillation spectrometry on a beta counter. The data are analysed using a non-linear, iterative curve-fitting computer program (Bowen & Jerman, *Trends Pharmacol. Sci.*, **16**, 413 (1995)) to determine the compound affinity parameter. The concentration of the compound needed to inhibit the [<sup>125</sup>I]DOI binding by 50% of the maximum is termed the IC<sub>50</sub> or K<sub>i</sub> value. Compounds are considered to possess high affinity for the 5HT<sub>2</sub> receptor if their IC<sub>50</sub> or K<sub>i</sub> values are ≤50 nM.



**5HT<sub>2</sub> Functional Assay: Phosphoinositide (PI) turnover assay**

The relative agonist activity of serotonergic compounds at the 5HT<sub>2</sub> receptor can be determined in vitro using the ability of the compounds to stimulate the production of [<sup>3</sup>H]inositol phosphates in [<sup>3</sup>H]myo-inositol-labeled A7r5 rat vascular smooth muscle cells by their ability to activate the enzyme phospholipase C. These cells are grown in culture plates, maintained in a humidified atmosphere of 5% CO<sub>2</sub> and 95% air and fed semi-weekly with Dulbecco's modified Eagle medium (DMEM) containing 4.5 g/l glucose and supplemented with 2mM glutamine, 10 µg/ml gentamicin, and 10% fetal bovine serum. For the purpose of conducting the phosphoinositide (PI) turnover experiments, the A7r5 cells are cultured in 24-well plates as previously described (Griffin et al., *J. Pharmacol. Expt. Ther.*, **286**, 411 (1998)). Confluent cells are exposed for 24-30 hrs to 1.5 µCi [<sup>3</sup>H]-myo-inositol (18.3 Ci/mmol) in 0.5 ml of serum-free medium. Cells are then rinsed once with DMEM/F-12 containing 10 mM LiCl prior to incubation with the test agent (or solvent as the control) in 1.0 ml of the same medium for 1 hr at 37°C, after which the medium is aspirated and 1 ml of cold 0.1 M formic acid added to stop the reaction. The chromatographic separation of [<sup>3</sup>H]-inositol phosphates ([<sup>3</sup>H]-IPs) on an AG- 1-X8 column is performed as previously described (Griffin et al., *J. Pharmacol. Expt. Ther.*, **286**, 411 (1998)) with sequential washes with H<sub>2</sub>O and 50 mM ammonium formate, followed by elution of the total [<sup>3</sup>H]-IPs fraction with 1.2 M ammonium formate containing 0.1 M formic acid. The eluate (4 ml) is collected, mixed with 15 ml scintillation fluid, and the total [<sup>3</sup>H]-IPs determined by scintillation counting on a beta-counter. Concentration-response data are analyzed by the sigmoidal fit function of the Origin Scientific Graphics software (Microcal Software, Northampton, MA) to determine agonist potency (EC<sub>50</sub> value) and efficacy (E<sub>max</sub>). Serotonin (5HT) is used as a positive control (standard) agonist compound and the efficacy of test compounds is compared to that of 5HT (set at 100%). The concentration of the compound needed to stimulate the production of [<sup>3</sup>H]-IPs by 50% of the maximum response is termed the EC<sub>50</sub> value. Compounds are considered potent agonists if their EC<sub>50</sub> values in this functional assay are ≤ 1 µM and are considered full agonists if their efficacy is > 80% of that of 5HT.

The above procedures were used to generate the data shown in Table 1.

**Table 1. 5HT<sub>2</sub> Receptor Binding and Functional Data for Representative Compounds.**

Compound	IC <sub>50</sub> , nM (SEM)	EC <sub>50</sub> , nM (SEM)	Efficacy (E <sub>max</sub> , %)
(R)-DOI	0.5 ± 0.2	277 ± 35	82
α-Methylserotonin	3.5 ± 0.9	189 ± 26	104
5-Methoxy-α-methyltryptamine	2.5 ± 0.9	286 ± 39	107
Serotonin	0.8 ± 0.2	338 ± 27	100

### **Acute IOP Response in Lasered (Hypertensive) Eyes of Conscious Cynomolgus Monkeys**

Intraocular pressure (IOP) was determined with an Alcon Pneumatonometer after light corneal anesthesia with 0.1% proparacaine. Eyes were washed with saline after each measurement. After a baseline IOP measurement, test compound was instilled in one 30 µL aliquot to the right eyes only of nine cynomolgus monkeys. Vehicle was instilled in the right eyes of six additional animals. Subsequent IOP measurements were taken at 1, 3, and 6 hours.

The profile of the IOP response following topical administration for each of these Compounds is provided in Table 2.

**Table 2. IOP Response for Representative Compounds**

Example	Dose, µg	Baseline IOP (mmHg)	Percent IOP Reduction ± SEM Hours after dose		
			1	3	6
(R)-DOI	100	31.9	11.0 ± 4.98	25.3 ± 2.97	34.4 ± 4.98
α-Methylserotonin	250	41.8	14.2 ± 4.39	25.8 ± 5.16	30.8 ± 7.72
5-Methoxy-α-methyltryptamine	300	38.1	21.6 ± 5.05	35.2 ± 6.12	33.4 ± 5.39
Serotonin	250	33.5	13.3 ± 5.31	18.0 ± 5.12	2.0 ± 7.39

The following topical ophthalmic formulations are useful according to the present invention administered 1-4 times per day according to the discretion of a skilled clinician.

**EXAMPLE 2**

<b>Ingredients</b>	<b>Amount (wt %)</b>
5HT <sub>2</sub> Compound	0.01 – 2%
Hydroxypropyl methylcellulose	0.5%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

**EXAMPLE 3**

<b>Ingredients</b>	<b>Amount (wt %)</b>
5HT <sub>2</sub> Compound	0.01 – 2%
Hydroxypropyl methylcellulose	0.5%
Cremophor EL	0.1%
Tromethamine, USP, AR	0.64%
Mannitol, USP	3.0%
Boric acid, USP	0.3%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

**EXAMPLE 4**

<b>Ingredients</b>	<b>Amount (wt %)</b>
5HT <sub>2</sub> Compound	0.01 – 2%
Methyl cellulose	4.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

5

**EXAMPLE 5**

<b>Ingredients</b>	<b>Amount (wt %)</b>
5HT <sub>2</sub> Compound	0.01 – 2%
Hydroxypropyl- $\beta$ -cyclodextrin	4.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

**EXAMPLE 6**

10

<b>Ingredients</b>	<b>Amount (wt %)</b>
5HT <sub>2</sub> Compound	0.01 – 2%
Xanthan gum	0.5-6.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

**EXAMPLE 7**

<b>Ingredients</b>	<b>Amount (wt %)</b>
5HT <sub>2</sub> Compound	0.01 – 2%
Guar gum	0.4- 6.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

5

**EXAMPLE 8**

<b>Ingredients</b>	<b>Amount (wt %)</b>
5HT <sub>2</sub> Compound	0.01 – 2%
Tyloxapol	0.2 – 4.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

10

**EXAMPLE 9**

<b>Ingredients</b>	<b>Amount (wt %)</b>
5HT <sub>2</sub> Compound	0.01 – 2%
White petrolatum and mineral oil and lanolin	Ointment consistency
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4

5

**EXAMPLE 10**

<b>Ingredients</b>	<b>Amount (wt %)</b>
5HT <sub>2</sub> Compound	0.01 – 2%
Brimonidine	0.2%
Hydroxypropyl methylcellulose	0.5%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

**We Claim:**

1. A method for treating glaucoma which comprises administering to a person in need thereof, a composition comprising a pharmaceutically effective amount of a compound with  
5 5HT<sub>2</sub> receptor agonist activity.

2. The method of Claim 1 wherein the 5HT<sub>2</sub> receptor agonist is present at a concentration of 0.01 weight percent to 5 weight percent.

10 3. The method of Claim 2 wherein the concentration is 0.25 weight percent to 2 weight percent.

4. The method of Claim 1 wherein the 5HT<sub>2</sub> receptor agonist is (R)-DOI,  $\alpha$ -Methylserotonin, 5-Methoxy- $\alpha$ -methyltryptamine.

15 5. The method of Claim 1 wherein the composition additionally comprises another compound selected from the group consisting of  $\beta$ -blockers, prostaglandins, carbonic anhydrase inhibitors,  $\alpha_2$  agonists, and miotics.

20 6. The method of Claim 5 wherein the compound is an  $\alpha_2$  agonist.

7. The method of Claim 6 wherein the  $\alpha_2$  agonist is selected from the group consisting of apraclonidine and brimonidine.

25 8. A composition for treating glaucoma comprising a pharmaceutically effective amount of a compound with 5HT<sub>2</sub> receptor agonist activity.

9. The composition of Claim 8 wherein the 5HT<sub>2</sub> receptor agonists concentration is 0.01 weight percent to 5 weight percent.

10. The composition of Claim 9 wherein the concentration is 0.25 weight percent to 2 weight percent.

11. The composition of Claim 8 wherein the 5HT<sub>2</sub> receptor agonist is selected from the group consisting of (R)-DOI,  $\alpha$ -Methylserotonin, 5-Methoxy- $\alpha$ -methyltryptamine.

12. The composition of Claim 8 wherein the composition additionally comprises another compound selected from the group consisting of  $\beta$ -blockers, prostaglandins, carbonic anhydrase inhibitors,  $\alpha_2$  agonists, and miotics.

13. The composition of Claim 12 wherein the compound is an  $\alpha_2$  agonist.

14. The composition of Claim 13 wherein the  $\alpha_2$  agonist is selected from the group consisting of apraclonidine and brimonidine.